In summary, epothilones and taxol have similar modes of action by stabilizing polymerization of microtubules. However, epothilones and taxol have distinct novel chemical structures.

MDR cells are 1500-fold more resistant to taxol (CCRF-CEM/VBL cells), epothilone A showed only 8-fold resistance and epothilone B showed only 5-fold resistance. For CCRF-CEM cells, Epo B is 6-fold more potent than Epo A and 10-fold more potent than Taxol. Desoxyepothilone B and compd #24 are only 3-4-fold less potent than Taxol and compound #27 is >2-fold more potent than Taxol. Finally, Taxol and vinblastine showed antagonism against CCRF-CEM tumor cells, whereas the combination of Epo B + vinblastine showed synergism.

Relative Cytotoxicity of Epothilones against Human Leukemic Cells *in Vitro* is in the order as follows:

CCRF-CEM Leukemic Cells

Epo B (IC_{50}=0.00035μM; Rel. Value=1) > VBL(0.00063;1/1.8) > #27(0.0010;1/2.9) > Taxol (0.0021; 1/6) > Epo A (0.0027; 1/7.7) > #24(0.0078; 1/22.3) > #10 (0.0095; 1/27.1) > #25 (0.021; 1/60) > #1 (0.022; 1/62.8) > #20 (0.030; 1/85.7) >#6 (0.052; 1/149) >#26 0.055; 1/157) >#17 (0.090; 1/257) >VP-16 (0.29; 1/8.29) >#15 (0.44; 1/1257) >#19 (0.96; 1/2943)

CCRF-CEM/VBL MDR Leukemic Cells

Epo B (0.0021; 1/6* [1]**) > #27 (0.0072; 1/20.6) > #1 (0.012; 1/34.3) > #10 (0.017; 1/48.6) > Epo A (0.020; 1/57.1 [1/9.5]) >#6 (0.035) > #20 (0.049) > #24 (0.053) > #25 (0.077) > #22 (0.146) > #26 (0.197) > #17 (0.254) >#11 (0.262) > VBL (0.332; 1/948.6 [1/158.1]) >Taxol (4.14; 1/11828 [1/1971.4]) > VP-16 (10.33; 1/29514 [1/4919])

*Potency in parentheses is relative to Epo B in CCRF-CEM cells.

**Potency in square brackets is relative to Epo B in CCRF-CEM/VBL MDR cells.

As shown in Table 9, treatment of MX-1 xenograft-bearing nude mice with desoxyepothilone B (35mg/kg, 0/10 lethality), taxol (5mg/kg, 2/10 lethality; 10mg/kg, 2/6 lethality) and adriamycin (2mg/kg, 1/10 lethality; 3mg/kg, 4/6 lethality) every other day, i.p. beginning day 8 for 5 doses resulted in a far better therapeutic effect for desoxyepothilone B at 35 mg/kg than for taxol at 5 mg/kg and adrimycin at 2mg/kg with tumor volume reduction of 98%, 53% and 28%, respectively. For the desoxyepothilone B-treated group, 3 out of 10 mice were found with tumor non-detectable on day 18. (See Fig. 46)

Extended treatment with desoxyepothilone B (40mg/kg, i.p.) beginning day

Table 17. Therapeutic Effects of Desoxyepothilone B, Taxol in Nude Mice Bearing MX-1 Xenograft.

				Treatment Schedule											# Died of toxicity
CONTROL															0/10
Day	8	10	12	14	16	18	20								
Tumor Size	19	78	151	372	739	1257	1991	Sacrificed (n = 10)							
(mm^3)	±2	±8	±15	±55	±123	±184	±331								
DESOXYEPOTHILONE B															0/10
Dose Schedule	35mg/kg on day					40mg/kg on day				No Treatment					
Day	8	10	12	14	16	18	20	22	24	26	28	30	45	47	50	60
Tumor Size																
Mouse 1	15	15	40	40	15	32	30	30	30	30	0	0	0	24	S*	—
Mouse 2	23	23	15	15	15	15	30	48	48	0	30	48	900	1200	S	—
Mouse 3	15	60	90	105	105	126	96	150	180	0	48	64	600	600	S	—
Mouse 4	21	38	38	0	0	10	8	8	8	8	0	0	0	0	0	0
Mouse 5	12	23	50	12	0	4	0	0	0	0	0	0	0	0	0	0
Mouse 6	15	40	32	8	8	8	8	12	12	12	12	30	120	120	S	—
Mouse 7	21	30	15	15	8	8	8	8	8	8	8	8	180	280	S	—
Mouse 8	20	48	70	15	15	8	8	0	0	0	0	0	0	8	S	—
Mouse 9	25	50	40	15	8	0	0	0	0	0	0	0	0	0	4	4
Mouse 10	20	38	38	38	38	25	25	25	0	0	15	15	100	100	S	—
TAXOL																2/10
Dose Schedule	5mg/kg on day					5mg/kg on day										
Day	8	10	12	14	16	18	20	22	24	26	28	30	45	47	50	60
Tumor Size	17	45	54	128	311	596	1114	1930	2285	S	(n = 10)					
	±2	±7		±13	±42	±115	±151	±346	±569	±597						
						Extended studies				→	Extended observations			→	Experiment ended	

*S: Sacrificed due to tumor burden